The Pending Claims

Claims 20-27 are currently pending and are directed to the method of inhibiting therapeutically or prophylactically a viral infection of a host. For the convenience of the Examiner, a set of pending claims is submitted herewith.

The Office Action

The Office has rejected claims 20-27 under 35 U.S.C. § 112, first paragraph. Claims 20 and 21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20-24 of Application No. 09/428,275. Claims 20 and 21 have been further rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876. Reconsideration of these rejections is hereby requested.

Discussion of Rejection under 35 U.S.C. § 112, first paragraph

Claims 20-27 have been rejected under Section 112, first paragraph, for alleged lack of enablement. This rejection is traversed for the reasons set forth below.

The Office contends that the instant specification provides insufficient guidance as to which regions of the cyanovirin peptide (i.e., which fragments of at least nine contiguous amino acids of SEQ ID NO: 2) are required for antiviral activity. Applicant respectfully submits that one of ordinary skill in the art, upon reading the specification, would be able to make an antiviral agent as recited in the pending claims and use it in the present inventive method. For example, Applicant provides nucleic acid and amino acid sequences encoding cyanovirins and fragments thereof in SEQ ID NOS: 1-4 and Figure 2. Applicant not only teaches and describes the nucleotide and amino acid sequences of cyanovirin, but teaches that the native cyanovirin is only 101 amino acids in length (specification at, e.g., page 16, lines 10-23) and that the amino acid sequence of cyanovirin is unique (specification at, e.g., page 16, lines 10-23) with no more than 8 contiguous amino acids of the native cyanovirin having been found in any known protein, such that there are no known proteins with greater than 13% sequence homology to the native cyanovirin. Recombinant production is set forth in the specification at, for example, page 18,

line 9, through page 19, line 11, and in Example 4, whereas nonrecombinant production, e.g., synthesis, is set forth in the specification at, for example, page 19, lines 12-19, and in Examples 2 and 3, with further discussion of recombinant and nonrecombinant production set forth at page 20, line 20 *et seq*. Antiviral protein conjugates and antiviral peptide conjugates, as well as methods of making such conjugates, are enabled by the specification at, for example, page 12, lines 16-33, and page 16, line 35, through page 21, line 22.

Methods of testing proteins and peptides comprising at least nine contiguous amino acids of SEQ ID NO: 2, as well as conjugates thereof, for antiviral activity are fully described in the instant specification at, for instance, page 24, line 19, through page 25, line 25, and in Examples 5 and 6. Thus, one of ordinary skill in the art, having the complete nucleotide and amino acid sequences of cyanovirin, SEQ ID NO: 2 of which is only 101 amino acids in length, would be able to generate nucleic acids encoding antiviral proteins and antiviral peptides comprising at least nine contiguous amino acids of SEQ ID NO: 2 and to screen them for antiviral activity using routine methods as taught by the specification.

It is well-established in patent law that "screening" constitutes routine experimentation. Routine experimentation, of course, is *not* undue experimentation.

The Office also contends that, given the unrelatedness of enveloped viruses, it is unlikely that cyanovirins would be capable of binding to viruses other than HIV-1 (Office Action, page 3, Section 3). However, Applicant has, indeed, demonstrated that cyanovirins are capable of binding viruses other than HIV. Using routine methods (e.g., ELISA and affinity chromatography) that were readily available before 1995, it has been demonstrated that cyanovirins bind viral surface glycoproteins other than gp120 of HIV, as evidenced by the Declaration under 37 C.F.R. § 1.132, of Dr. Michael R. Boyd, submitted herewith. As set forth by Dr. Boyd, cyanovirins bind to the surface glycoprotein gp1-Z of the Ebola virus and the gC glycoprotein of the virus *Herpes simplex* (HSV). It has been further demonstrated that cyanovirins are able to bind to the carbohydrate moieties of viral surface glycoproteins from which the proteinaceous component has been removed. Thus, it is reasonable for the ordinarily skilled artisan to expect that cyanovirins can bind a wide array of pathogens, such as viruses, comprising surface carbohydrate moieties, such as glycoproteins.

The Office additionally alleges that the instant specification fails to provide guidance pertaining to the ability of cyanovirins to inactivate natural HIV, as opposed to laboratory strains of HIV. On the contrary, the specification clearly discloses that cyanovirins can target a broad range of viruses, including *clinical and laboratory* strains (see specification at, for instance, page 18, lines 16-23). In addition, the specification discloses that all tested strains (e.g., clinical and laboratory strains) of HIV-1, HIV-2 and SIV were similarly sensitive to cyanovirins (see specification at, for example, page 21, lines 9-22). Indeed, the present inventive method overcomes many of the obstacles associated with antiviral therapies by effectively destroying or rendering non-infectious both laboratory and *all* tested clinical strains of HIV.

Further, according to the Office, the disclosure fails to provide guidance pertaining to the immunologic properties of cyanovirins in a host. The specification provides sufficient guidance with respect to formulations and routes of administration of cyanovirin peptides and fragments thereof, including guidance regarding evasion of a host immunogenic reaction. For example, the specification teaches that site-specific delivery of the therapeutic agent or induction of tolerance by initially administering low doses of antiviral agent can aid in avoiding untoward immune reactions (see specification at, for example, page 25, line 19, through page 26, line 9).

It appears that the remainder of the Office's rejection centers on the assertion that one of ordinary skill in the art would not expect that the antiviral protein, the antiviral peptide, the antiviral protein conjugate or the antiviral peptide conjugate can inhibit prophylactically or therapeutically a viral infection as claimed (Office Action, pages 3-5, Section 6). The Office further contends that the working examples of the instant application are not sufficient to enable the pending claims, and that the experiments described in the Declaration Under 37 C.F.R. § 1.132 submitted February 1, 2001, does not accurately predict clinical efficacy (Office Action, pages 3-7, Sections 6 and 8).

Contrary to the assertion of the Office, one of ordinary skill in the art, using the instant specification as a guide, would be able to practice the claimed method of inhibiting prophylactically or therapeutically a viral infection in a host. The specification fully enables and describes formulations comprising a cyanovirin or conjugate thereof. The specification further discloses effective concentrations of cyanovirins and correlates those concentrations

with antiviral activity in an *in vitro* assay widely accepted by those of ordinary skill in the art as predictive of *in vivo* results (see, for example, page 21, line 23, through page 22, line 6, and Examples 5 and 6). No further demonstration is required (*see* PTO Examination Guidelines on Utility Requirement, 50 PTCJ at 307, left column). As such, sufficient guidance is provided in the instant specification as to how to achieve inhibition of a viral infection in a host using the present inventive method and formulation with a reasonable expectation of success.

In addition to the *in vitro* assays described in the instant specification, Applicant has demonstrated that cyanovirins can inhibit a viral infection *in vivo* using a macaque animal model. Yet, the Office contends that the animal model used is not predictive of clinical results, and cites numerous references in support of its contention. However, one of the references cited by the Office, namely Allan (Chapter 1.2, *AIDS: Biology, Diagnosis, Treatment and Prevention, fourth edition*, DeVita et al., Eds., Lippincott-Raven Publishers (1997)), characterizes the macaque animal model as "an important animal model" (page 15, 1st col.). In fact, Allan states that models using SHIV can be used to determine "whether the animal is protected from infection as determined by virus isolation, antibody responses, and detection of viral DNA in tissues by polymerase chain reaction" and that recombinants between HIV and $SIV_{smm/mac}$ "are reasonable choices in the design of such experiments" (page 23, 2nd col., lines 1-7).

Another alleged disadvantage cited by the Office with respect to the animal model of the Rule 132 Declaration is that there is currently no disease association with the SIV/SHIV model. This is of no import as the pending claims are directed to inhibition of viral infection. Cyanovirins successfully inhibited viral infection in a clinically relevant animal model, as set forth in the Rule 132 Declaration, thereby demonstrating that the antiviral agent of the present inventive method can achieve the claimed biological effect.

Applicant further notes that the reported setbacks involving animal models involve vaccine research. Yet, the pending claims are directed to a method of inhibiting a viral infection comprising administering to the host an antiviral effective amount of an isolated and purified antiviral agent, not protection upon antigen challenge as is the case with vaccines.

The Office further contends that insufficient guidance is provided concerning the ability of cyanovirins to inactivate physiological relevant concentrations of HIV-1, HIV-2, or

other viruses. First, the dose of virus effectively blocked from infecting the animal subjects was *known to produce 100% infectivity* in macaques via the route of administration utilized. Second, the Rule 132 Declaration submitted herewith evidences the ability of cyanovirins to bind viruses other than the particular virus used in the *in vivo* assay and the *in vitro* assays set forth in the instant specification. Thus, one of ordinary skill in the art would reasonably expect that cyanovirins effectively inhibit prophylactically or therapeutically a viral infection of a host.

Finally, the Office contends that the Rule 132 Declaration previously submitted is deficient in that it failed to measure reductions in viral load. However, the pending claims are directed to a method of inhibiting a viral infection of a host. The results described in the Rule 132 Declaration demonstrate that cyanovirins successfully inhibited a viral infection due to inoculation of SHIV89.6P intrarectally or intravaginally, respectively. All treated animals were protected from viral infection, as demonstrated by the absence of viral isolates and viral DNA in blood samples. Thus, the ability of the antiviral peptides and antiviral proteins of the present inventive method to inhibit a viral infection has been proven.

The Office further contends that the experimental model of the previously submitted Rule 132 Declaration failed to measure reductions in viral load. The Office alleges that it seems unlikely that adequate concentrations of cyanovirin can be maintained over sufficient periods of time to provide any meaningful effect. However, the precise dosing regimen for administering cyanovirin to reduce viral load can be easily determined by the ordinarily skilled artisan using only routine methods, as attested to by Dr. Michael Boyd (see Declaration Under 37 C.F.R. § 1.132, submitted herewith). Indeed, clinicians routinely monitor viral load to tailor antiviral therapy for patient-specific care. A range of appropriate doses of cyanovirin are provided in the instant specification and timing of administration can easily be determined by the ordinarily skilled artisan by performing a standard dose response study, which merely entails administering a dose of cyanovirin to a host and measuring viral load. Methods of determining viral load in a host are well within the skill in the art. Thus, using routine clinical laboratory techniques, the ordinarily skilled artisan can determine an appropriate dosage regimen to maintain sufficient cyanovirin concentrations in a host to realize a biological effect (e.g., a therapeutic effect as evidenced by a reduction in viral load).

In summary, all that is required to satisfy the enablement requirement is that the instant specification teaches how to make and use the presently claimed invention. The instant specification clearly provides sufficient guidance as to enable the ordinarily skilled artisan to practice the present invention as claimed. For the above reasons, the rejected claims are, in fact, enabled. Accordingly, Applicant requests withdrawal of this rejection.

Discussion of Provisional Obviousness-Type Double Patenting Rejection

Claims 20 and 21 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 20-24 of Application No. 09/428,275. This rejection will be addressed upon indication of allowable subject matter.

Discussion of Obviousness-Type Double Patenting Rejection

Claims 20 and 21 have been further rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876 ("the '876 patent"). This rejection is traversed for the reasons set forth below.

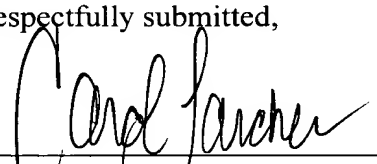
Instant claims 20 and 21 are directed to a method of inhibiting prophylactically or therapeutically a viral infection of a host. The method comprises administering to a host an antiviral effective amount of an isolated and purified antiviral agent selected from the group consisting of an antiviral protein, an antiviral peptide, an antiviral protein conjugate and an antiviral peptide conjugate. The antiviral protein or antiviral peptide is encoded by an isolated and purified nucleic acid molecule encoding at least nine contiguous amino acids of SEQ ID NO: 2, wherein the at least nine contiguous amino acids of SEQ ID NO: 2 have antiviral activity. Upon administration of the antiviral effective amount of the formulation, the viral infection is inhibited. Claims 13-19 of the '876 patent are directed to a method of contacting a virus with an antiviral agent. Claims 13-19 of the '876 patent do not teach or suggest administering the aforementioned antiviral agent to a host to inhibit prophylactically or therapeutically a viral infection in the host. In that there is no teaching or suggestion in

claims 13-19 of the '876 patent to administer the aforementioned antiviral agent to a host to inhibit a viral infection, instant claims 20 and 21 cannot be considered to constitute obviousness-type double patenting of claims 13-19 of the '876 patent, and the rejection should be withdrawn.

Conclusion

The application is considered to be in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: August 3, 2001